REMARKS

Reconsideration of the rejections set forth in the Office action mailed February 15, 2006 is respectfully requested, for the reasons discussed below. Claims 1-3, 5-11, and 19-27 are currently pending.

I. Amendments

In order to further distinguish the claimed subject matter over the cited art and thereby expedite allowance, claim 1 is amended to state that the mixture of "(i) the different substantially uncharged analyte molecules and (ii) the specific probe molecule" are applied to an ion exchange medium. Claims 15-17 are accordingly cancelled.

Claim 7 is amended to recite that the probe includes a sequence complementary to an N-1 internal deletion variant of the selected sequence. Support is found in parent claim 2, which recites that "each analyte molecule has a nucleotide sequence selected from the group consisting of a selected sequence, different length fragments of the selected sequence, internal deletion or insertion variants of the selected sequence, mutation variants of the selected sequence, and combinations thereof."

Claims 1 and 10 are also amended for clarity, as discussed below.

No new matter is added by the amendments.

II. Rejections under 35 U.S.C. §112, Second Paragraph

Claims 1-27 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (and its dependent claims) were rejected in view of the term "the different analyte molecules". This term has been clarified by amending it to recite "the different substantially uncharged analyte molecules", as recited earlier in the same clause of the claim.

Claim 10 was rejected in view of the term "said analysis" lacking antecedent basis. This term has been amended to "said applying and separating", as recited in steps (a) and (b) of the parent claim.

Claim 15 was rejected in view of the term "charge bearing support" lacking antecedent

basis. This claim has been cancelled, rendering the rejection moot.

In view of the foregoing, the applicants submit that the pending claims comply with the requirements of 35 U.S.C. §112, second paragraph.

III. Rejections under 35 U.S.C. §102(b)

Claims 1-3, 5-6, 10, 15-17, 19-20, and 23-24 were rejected under 35 U.S.C. §102(b) as being anticipated by Fuchs *et al.*, WO 97/12995. This rejection is respectfully traversed for the following reasons.

A. The Claims

Independent claim 1, as presented above, is directed to:

a method of separating a population of duplexes, each comprising one of a population of different, substantially uncharged oligomeric analyte molecules and a specific probe molecule,

wherein the substantially uncharged analyte molecules are oligonucleotide analogs composed of linked subunits of which at least 90% are uncharged, and the specific probe molecule is a fully charged nucleic acid or fully charged nucleic acid analog,

the method comprising:

(a) applying to an ion exchange medium a mixture of (i) the different substantially uncharged analyte molecules and (ii) the specific probe molecule, under conditions such that the probe molecule forms stable duplexes with a plurality of or all of the different substantially uncharged analyte molecules,

thereby forming a plurality of different probe-analyte duplexes, which differ from each other with respect to the presence, length or position of an unhybridized portion of the probe molecule, and

(b) *separating the different probe-analyte duplexes from each other* and from single stranded analyte or probe molecules within the medium.

B. The Cited Art

Fuchs *et al.* describes methods for detecting and/or separating a nucleic acid having a selected target sequence in a nucleic acid-containing sample, by hybridizing the target nucleic acid with a complementary PNA (peptide nucleic acid) probe, which is typically labeled to

facilitate detection. By employing a PNA as the probe molecule, the hybridization can be carried out under conditions such that the PNA/DNA duplex is stable, but the corresponding DNA/DNA duplex is not (see, for example, page 7, lines 14-24 of the PCT publication).

The majority of the description in Fuchs *et al.* is concerned with the use of a single PNA probe, to detect a particular nucleic acid target sequence. This portion of the disclosure does not anticipate the present claims, which require "a population of different, substantially uncharged oligomeric...molecules".

The use of two different PNA probes is discussed in Fuchs *et al.* at page 4, lines 21-24, as cited by the Examiner:

"In yet other embodiments, the claimed invention relates to the above methods, compositions and apparatus wherein at least two PNA probes are labeled, each of which hybridizes with a different target sequence, if present, to form a detectable complex. The target sequences may be present on the same DNA segment or separate DNA segments...".

In the above scenario, if the different target sequences are present on "separate DNA segments", then the instant claim limitation of "a *specific* probe molecule" which is "a fully charged nucleic acid or fully charged nucleic acid analog" is not met, and the applicants' claims are not anticipated.

If the different target sequences are "present on the same DNA segment", the resulting structure could be depicted as follows:

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-------------------------------------------------- DNA
*********                  **********  two PNA's
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In order to correspond to the language of the applicants' claims, the two probe-hybridized regions on the single DNA segment, as depicted above, would have to be considered "a plurality of different probe-analyte duplexes". However, even if this were assumed, the reference does not show "separating said different probe-analyte duplexes *from each other*", as recited in the claim. Clearly, this would be impossible unless the single DNA segment were somehow cleaved between the two hybridized regions.

Since the reference does not disclose all of the elements set out above in claim 1 and its dependent claims, the claims cannot be anticipated by this reference under 35 U.S.C. §102(b).

In view of this, the applicant respectfully requests the Examiner to withdraw the rejection under 35 U.S.C. §102(b).

IV. Rejections under 35 U.S.C. §103(a)

Claims 7-9 and 11 were rejected under 35 U.S.C. §103(a) as being unpatentable over Fuchs *et al.*, cited above, in view of Cummins *et al.*, U.S. Patent No. 5,874,213, cited in a previous office action. This rejection is respectfully traversed for the following reasons.

A. The Claims

Dependent claims 7-9 and 11 recite that the (fully charged) probe includes a sequence complementary to an internal N-1 deletion variant of the selected (substantially uncharged) target sequence. In dependent claim 8, the length of the (fully charged) probe is also equal to the N-1 deletion variant of the target sequence. These claims otherwise include all the limitations of parent claim 1, discussed above.

These claims are directed to a particular embodiment in which the probe is designed to select for a particular N-1 deletion variant of the full length target sequence, as described in the specification at, for example, page 10, lines 26-32.

B. The Cited Art

As described above, the primary reference, Fuchs *et al.* does not teach the claimed step of "separating said different probe-analyte duplexes *from each other*" within an ion exchange medium, or any charge-bearing separation medium.

The Examiner points to a scenario shown in the Cummins patent, as discussed in previous responses, in which Cummins *et al.* "duplexes a single PNA probe (20-mer) with a 20-mer DNA; 19-mer DNA (N-1 variant); and 18-mer DNA (N-2 variant)" (Office Action, page 7). This scenario is shown, e.g., in Example 3 of the patent.

However, this Example does not indicate that either of the two deletion variants are internal deletion variants of the 20-mer DNA, or that the PNA probe includes a sequence complementary to, and/or the same length as, any internal deletion variant of the 20-mer DNA. Therefore, the Example is not pertinent to these dependent claims.

Accordingly, the applicants request that the rejection of these claims under 35 U.S.C. §103(a) be withdrawn.

Further observations regarding the rejection over Cummins

Applicants further contend that the claimed invention, even in its broadest aspect (i.e. claim 1), would not have been obvious over this combination of references. The Examiner has contended that, because the "separation [in Cummins *et al.*] is achieved, in part, by the difference in the sizes of the duplexes", a skilled person would "have a clear expectation of success at detecting a N-1 deletion variant DNA via use of PNAs of varying lengths", in view of the "differences in the sizes of the formed DNA/PNA duplexes" (Office Action, page 7).

This conclusion appears to be based on hindsight reasoning, in view of the success of the applicants' method. In fact, on page 8 of the Office Action, the Examiner points to the subject matter of applicants' claims 2 and 3 for support, as though these were part of the prior art, which is clearly improper.

In addition, the Examiner has misapplied the standard for *prima facie* obviousness, by focusing only on expectation of success, and neglecting the requirement that "there must be some suggestion or motivation, either in the references or in knowledge generally available to one skilled in the art, to modify a reference or combine reference teachings" (MPEP §2143). In the present case, to modify the Cummins reference as suggested by the Examiner, one would employ multiple "PNAs of varying lengths" to duplex with a single "N-1 deletion variant DNA" that was to be detected (Office Action, page 7). Based on the teachings of the reference, such a modification would only needlessly complicate the analysis and waste probe molecules; it would serve no purpose in detecting the target DNA. There would be no reason for a skilled person to make such a modification.

V. Further Rejections under 35 U.S.C. §103(a)

Claims 25-27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Fuchs *et al.*, cited above, in view of Ecker *et al.*, U.S. Patent No. 5,968,053. This rejection is respectfully traversed for the following reasons.

A. The Claims

Claims 25-26 recite that the DNA probe is labeled, and claim 27 recites isolating a probe-analyte duplex. They otherwise include all the limitations of parent claim 1, discussed above.

B. The Cited Art

Ecker *et al.* describe gel-shift motility assays in which a PNA is hybridized with its complementary DNA molecule. As stated, for example, at column 35, lines 23-31, the "DNA complement" to a PNA test molecule "was synthesized and labeled".

As discussed above, Fuchs *et al.* does not teach all the limitations of claim 1, and Ecker et al. does not make up for its deficiencies in this regard. Moreover, the situation described in Ecker *et al.* is entirely different from the procedures described in Fuchs *et al.*, where the DNA component is not specifically synthesized, but is present as a target sequence in a sample mixture of nucleic acids, e.g. a "genomic sample" (page 3, lines 15-16). It would clearly not be feasible or logical for a target DNA within such a sample mixture to be labeled.

Accordingly, the applicants request that the rejection of these claims under 35 U.S.C. §103(a) be withdrawn.

VI. Further Rejections under 35 U.S.C. §103(a)

Claims 21-22 were rejected under 35 U.S.C. §103(a) as being unpatentable over Fuchs *et al.*, cited above, in view of Iversen, U.S. Patent No. 6,365,351. This rejection is respectfully traversed for the following reasons.

Claims 21-22 recite that the analyte molecules are morpholino oligomers. They otherwise include all the limitations of parent claim 1, discussed above.

As discussed above, Fuchs *et al.* does not teach all the limitations of parent claim 1.

The Iversen reference, which discusses the formation of nucleic acid/morpholino heteroduplexes, does not describe the separation, on an *ion exchange medium, of a plurality of duplexes between different morpholino oligomers and a specific nucleic acid molecule. Therefore, this combination of references does not teach or suggest all the limitations of claim 1.

Accordingly, the applicants request that the rejection of these claims under 35 U.S.C. §103(a) be withdrawn.

VII. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

Respectfully submitted,

Date: Aug. 10, 2006

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